Journal of Surgical Oncology 63:240–248 (1996)

Preoperative Simultaneous Cisplatin- or Carboplatin-based Chemotherapy and Radiotherapy for Squamous Cell Carcinoma of the Oral Cavity

TADAAKI KIRITA, DDS, PhD, KAZUHIKO OHGI, DDS, MOTOKATSU TSUYUKI, DDS, PhD, NORIAKI KAMIKAIDO, DDS, PhD, KAZUHIKO YAMAMOTO, DDS, PhD, AND MASAHITO SUGIMURA, DDS, PhD
From the Department of Oral and Maxillofacial Surgery, Nara Medical University, Nara, Japan

Background: Encouraging results have been reported with cisplatin- or carboplatin-based chemotherapy regimens and simultaneous irradiation treatment in advanced and unresectable head and neck head and neck cancer. We have therefore examined the effectiveness of such therapy on tumor control, survival, and toxicity in patients with advanced oral squamous cell carcinoma.
Methods: Forty-one patients with squamous cell carcinoma of the oral cavity (including soft palate) were treated preoperatively with cisplatin or carboplatin, and 5-fluorouracil or peplomycin in combination with simultaneous irradiation to a target volume of 40Gy, and 2–6 weeks later, curative surgery was performed.
Results: Thirty-eight patients (91.7%) had Stage III or IV disease, and three patients had Stage II lesions. The preoperative clinical responses of the primary tumor were: 25 patients (61.0%) achieved a complete response (CR), 15 (36.6%) a partial response (PR), only 1 patient (2.4%) had stable disease or no change (NC). The overall response rate was 97.6%. Histological effects according to the grading system of Shimosato and coworkers [Jpn J Clin Oncol 1:19–35, 1971] were seen in 38/41 (92.7%). Of clinical CR patients, 73.9% were also histologic negative for tumor. Side effects of this therapy were relatively low and reversible. With a median follow-up of 52.8 months (range 17–92 months), 5-year cumulative survival rates were 81.5% for all patients, 100% for Stage II, 88.6% for Stage III, and 76.4% for Stage IV patients, respectively. There was no significant postoperative morbidity.
Conclusions: This preoperative chemoradiotherapy regimen was highly active, well tolerated, and appeared to have a survival benefit even for advanced carcinomas of the oral cavity.

KEY WORDS: **oral carcinoma, preoperative therapy, chemoradiotherapy, cisplatin, carboplatin, survival**

INTRODUCTION

In early stages, oral squamous cell carcinomas can be treated curatively by surgery or radiotherapy, but locally advanced cases are often not controlled by single-modality therapy. Radiotherapy in combination with radical

Accepted for publication August 26, 1996.

Address reprint requests to Tadaaki Kirita, Department of Oral and Maxillofacial Surgery, Nara Medical University, Shijocho, Nara-Kashiwara 634, Japan.

surgery constitutes a more effective approach to the treatment of advanced squamous cell carcinoma of the oral cavity. Whereas cures are also frequent with this approach in early stage disease, the success rate falls rapidly with advancing tumor stage. The incidence of locoregional failure following definitive local treatment with radiation and surgery in advanced head and neck cancer has been reported to be as high as 50% [1,2].

In recent years encouraging results have been reported with cisplatin- [3,4] or carboplatin- [5] based chemotherapy regimens and simultaneous irradiation as first-line treatment in advanced and unresectable head and neck cancer. Other studies [6,7] have reported that simultaneous chemoradiotherapy is effective in producing high rates of locoregional control and significantly improved survival rates. Such impressive results have suggested that the simultaneous administration of platinum derivatives and radiotherapy as a preoperative treatment in advanced operable oral squamous cell carcinoma also might be effective.

In this report we examine the effectiveness of simultaneous cisplatin- or carboplatin-based chemotherapy and radiotherapy on tumor control, survival, and toxicity in patients with advanced oral squamous cell carcinoma.

PATIENTS AND METHODS

Between May 1988, and June 1994, a total of 41 patients with previously untreated and clinically advanced squamous cell carcinoma of the oral region (including the soft palate) were eligible for this study. All patients had resectable disease before induction therapy and an ECOG (Eastern Cooperative Oncology Group criteria) performance status of 0–2. In all cases the diagnosis was confirmed histologically. Specifically excluded were patients with adenocarcinoma, second primaries, prior radiation, surgery or chemotherapy, and distant metastases. Pretreatment laboratory requirements included a leukocyte count of $> 4{,}000/mm^3$, platelet count $> 100{,}000/mm^3$, BUN < 20 mg/dl, serum creatinine < 1.5 mg/dl, and creatinine clearance > 60 ml/minute. Pretreatment evaluation also included a complete history and physical examination, routine chest radiograph, and liver function tests. Patients who received peplomycin (a bleomycin derivative) as part of their chemotherapy were all < 70 years old and underwent pulmonary function testing and were required to demonstrate a vital capacity $> 75\%$ normal, CO diffusion capacity $> 75\%$ normal, and/or $pO_2 > 80$ mmHg on room air. Patients who had significant weight loss or were anticipated to have such a loss during treatment had elective placement of a feeding tube and close monitoring of nutritional status.

All patients were staged according to the criteria laid down by the UICC on Cancer Staging (1987). Informed consent was obtained from all participating patients. The patient population consisted of 28 (68.3%) males and 13 (31.7%) females. The median age was 56.3 years (range 43–74 years) (Table I).

TABLE I. Patient Characteristics in Oral Squamous Cell Carcinoma (including soft palate)

No. of patients					41	
Female/male ratio					13/28	
Median age (yr)					56.3 (range 43–84)	
Median performance status					1 (range 0–2)	
Stage of disease						
	N0	N1	N2a	N2b	N2c	N3
T2	3	14	–	3	3	–
T3	1	5	1	–	–	–
T4	1	7	2	–	1	–
Tumor sites						
Tongue					16	
Upper gingiva					10	
Lower gingiva					6	
Floor of mouth					3	
Buccal mucosa					4	
Hard palate					1	
Soft palate					1	
Disease stage						
I					0	
II					3	
III					20	
IV					18	

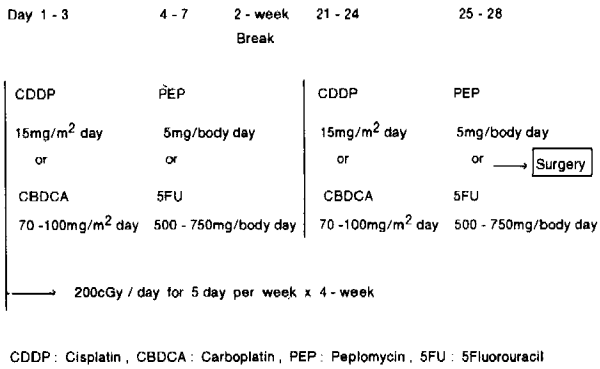

Fig. 1. Treatment schema. Radiation therapy and chemotherapy began on the same day. Cisplatin or Carboplatin was given on days 1–3 and 21–24, Peplomycin or 5-Fluorouracil was also given on days 4–7 and 25–28. Radiation therapy consisted 200cGy/day, 5 times/week for a total of 4,000cGy.

Treatment Plan

All patients were scheduled to receive 4,000 cGy (200 cGy daily fractions, 5 times a week) external beam irradiation to the primary tumor and regional lymphatics over a 4-week period. During the course of radiation therapy, cisplatin (15 mg/m^2) or carboplatin (70–100 mg/m^2) on days 1–3 and peplomycin (5 mg/day) or 5-fluorouracil (5-FU) (500–750 mg/day) on days 4–7 were administered intravenously (IV) or intra-arterially (IA). A second cycle of this regimen was repeated in the fourth week of radiation therapy (Fig. 1).

Patients selected for intra-arterial chemotherapy had advanced (Stage III or IV) primary oral carcinomas suitable for infusion via the external carotid artery. Catheterization was performed before chemoradiotherapy was started. Usually, under local anesthesia, the superficial temporal artery was isolated. Retrograde catheterization into the external carotid artery was performed until the tip of the catheter reached the desired position level. Intraoperative evaluations of the good positioning of the catheter were performed with direct injection in the catheter of dyes (Patent blue), which produced direct painting of the tumor or of the corresponding mucosal and cutaneous area. In case of lesions reaching the median line, a bilateral catheterization was performed. The catheters were left in place for 4 weeks.

Curative surgery was performed 2–6 weeks after the end of chemoradiotherapy when the treatment-related acute toxicities had almost disappeared. The surgical decision was based on the pretreatment staging, and the surgery consisted of a composite resection of any residual primary tumor with immediate reconstruction, if possible. The accurate assessment to ensure satisfactory tumor resection was achieved by combining visual examination with careful palpation and the taking of frozen sections during the operation. Radical neck dissections were done on all patients with clinically positive neck nodes. On the patients with T3 or T4 primary tumors and clinically negative necks, ipsilateral radical neck dissections or functional neck dissections were also done because of the risk of occult lymphatic metastases.

Treatment Response/Toxicity

Evaluation of the clinical response to preoperative chemoradiotherapy was assessed immediately prior to surgery. Clinical responses were defined as: complete response (CR), complete clinical regression of tumor; partial response (PR), >50% reduction in the cross-sectional area of measurable tumor using the product of the two largest perpendicular diameters; no change (NC), reduction < 50% or increase < 25% in the size of measurable tumor; progressive disease (PD), an increase of > 25% in such measurements.

Histologic responses were defined on the basis of the grading system of Shimosato and coworkers [8] (Table II) using semiserial sections of whole surgical specimens. The histologic grade of regression was classified according to a four-stage scale with some subclassifications. Grade I or Grade IIa indicates almost certain regrowth of the tumor; Grade IIb, possible recurrence; Grades III and IV, small probability of recurrence with a chance for local cure. The histologic grades of regression were divided into two groups in terms of a good (Grades IIb, III, IVa,b,c) and poor (Grade I, IIa) response to combined chemoradiotherapy.

Differences in initial response rates were evaluated by the Chi-square test and toxicity was assessed by worst event for each organ system according to the WHO scale [9].

Survival curves were constructed using the Kaplan-Meier method, and these curves were compared using the log-rank test. Survival times were calculated from the date chemoradiotherapy was initiated and were analyzed as of December 31, 1995.

RESULTS

All patients were evaluable for clinical and histologic response, toxicity, and survival. The median follow-up was 52.8 months (range, 17 to 92 months).

Twenty-eight of 41 patients (68.3%) completed the full preoperative treatment regimen as planned. Another 13 patients (31.7%) received a total of 4,000 cGy radiotherapy, but only a single cycle of chemotherapy. In 29 of 41 patients (70.3%), cisplatin or another anticancer agent was administered by the intra-arterial route and intravenous route in the remaining 12 patients (29.3%). The chemotherapy regimens and the number of the patients are: cisplatin + peplomycin, 34 patients (82.9%), cisplatin + 5-FU, 3 patients (7.3%), carboplatin + peplomycin, 2 patients (4.9%), carboplatin + 5-FU, 2 patients (4.9%), respectively.

Clinical Response

The overall clinical response rate for primary tumors was as follows: 25 of 41 patients (61.0%) had a complete response (CR) and 15 of 41 (36.6%) a partial response (PR) for a total response rate (CR + PR) of 97.6% (40 of 41 patients). One patient (2.4%) had no change in his tumor burden (NC), and no patients had progression of disease on this study. There was no significant difference in the overall response rate in terms of disease site (Table III). Clinical responses as a function of the primary tumor (T) and nodal (N) stage were also examined (Table IV). The CR rate was higher for T2 patients (73.9%) than for T3 and T4 patients (42.9% and 45.5%, respectively), although there were no significant differences in overall response rates that ranged from 95.6% to 100%. The overall response rate for patients with clinically positive lymphatic metastase was only 50.0% (18/36) with 5 of 36 patients (13.9%) having a CR and 13 (36.1%) having a PR.

Clinical responses for different amounts of chemotherapy administered and different routes of administration were also examined (Table V). The CR rate was slightly higher for IA (58.6%) than IV (50.0%), although the overall response rate was essentially the same. The CR rate was higher for two than one cycle of chemotherapy ($P < .05$), and although the overall response rate was slightly higher for two cycles of chemotherapy, the differ-

TABLE II. Grading of Histologic Regression to Preoperative Chemoradiotherapy in Oral Carcinoma (including soft palate)

Grade I	Characteristic changes are noted in tumor cells, but tumor structures have not been destroyed (there is no defect in tumor nests resulting from the lysis of individual tumor cells).
Grade II	In addition to characteristic cellular changes, tumor structures have been destroyed as a result of the disappearance of tumor cells. However, variable number of "viable cells" still remain.
a.	Destruction of tumor structures is of a mild degree, i.e., "viable tumor cells" are frequently observed.
b.	Destruction of tumor structures is of a severe degree, i.e., "viable tumor cells" are few in number.
Grade III	Markedly altered, presumably non-viable tumor cells, are present singly or in small clusters and "viable cells" are hardly seen.
Grade IV	No tumor cells remain in any sections (local cure).
a.	Extensive areas of coagulation necrosis are present.
b.	Granulation tissue with or without small foci of necrosis including keratotic debris remains.
c.	Only cicatrix is observed.

TABLE III. Clinical Response by Site of Primary Tumor in Oral Carcinoma (including soft palate) to Preoperative Chemoradiotherapy

	Response			
Site	CR[a]	PR[b]	NC[c]	CR + PR(%)
Tongue	11	4	1	93.8
Upper gingiva	6	4	–	100
Lower gingiva	1	5	–	100
Floor of mouth	3	1	–	100
Buccal mucosa	2	1	–	100
Hard palate	1	–	–	100
Soft palate	1	–	–	100
Total	25	15	1	97.6
(%)	(61.0)	(36.6)	(2.4)	(Average)

[a]Complete response.
[b]Partial response.
[c]No change.

TABLE IV. Clinical Response by Primary Tumor (T) Category and Node (N) Stage in Oral Carinoma (including soft palate) to Preoperative Chemoradiotherapy

	CR[a] (%)	PR[b] (%)	NC[c] (%)	Total
T2	17 (73.9)	5 (21.7)	1 (4.3)	23
T3	3 (42.9)	4 (57.1)	–	7
T4	5 (45.5)	6 (54.5)	–	11
N1	4 (15.4)	10 (38.5)	12 (46.1)	26
N2a	1 (33.3)	1 (33.3)	1 (33.3)	3
N2b	0 (0)	0 (0)	3 (100.0)	3
N2c	0 (0)	2 (50.0)	2 (50.0)	4

[a]Complete response.
[b]Partial response.
[c]No change.

TABLE V. Clinical Response of Primary Tumors to Various Chemotherapy Regimens/Mode of Administration in Oral Carcinoma (including soft palate)

	CR[a] (%)	PR[b] (%)	NC[c] (%)	Total
CDDP[d]/PEP[e]	24 (66.7)	12 (33.3)	–	36
CDDP[d]/5FU[f]	1 (33.3)	2 (66.7)	–	3
CBDCA[g]/PEP[e]	–	1 (50.0)	1 (50.0)	2
IA	19 (58.6)	9 (37.9)	1 (3.5)	29
IV	6 (50.0)	6 (50.0)	–	12
1-cycle	4 (30.8)	8 (61.5)	1 (7.7)	13
2-cycle	20 (71.4)*	8 (28.6)	–	28

IA: Intra-arterial
IV: Intravenous
*$P < .025$

[a]Complete response.
[b]Partial response.
[c]No change.
[d]Cisplatin.
[e]Peplomycin.
[f]5-Fluorouracil.
[g]Carboplatin.

TABLE VI. Relationship Between Histologic Regression Grade and Clinical Response to Preoperative Chemoradiotherapy in Oral Carcinoma (including soft palate)

Grade	CR[a]	PR[b]	NC[c]	Total (%)
I	–	–	–	–
IIa	–	2	1	3 (7.3)
IIb	2	9	–	11 (26.8)
III	4	4	–	8 (19.5)
IV	17	2	–	19 (46.4)

[a]Complete response.
[b]Partial response.
[c]No change.

ence was not significant ($P > .1$). In general, there was no significant difference in overall clinical response rates as a function of the chemotherapy regimen.

Histologic Response

The histologic regression grade was determined in all 41 patients (Table VI). Thirty-eight (Grades IIb: 11, III:

TABLE VII. Toxicity Grading of Preoperative Chemoradiotherapy in Oral Carcinoma (including soft palate)

	Grade				
Toxicity	0	1	2	3	4
Hematologic					
Leukocites	21 (51.2%)	3 (7.3%)	15 (36.6%)	2 (4.9%)	–
Platelets	39 (95.2%)	1 (2.4%)	1 (2.4%)	–	–
Hemoglobin	34 (82.9%)	4 (9.8%)	2 (4.9%)	1 (2.4%)	–
Gastrointestinal					
Nausea/vomiting	29 (70.7%)	9 (22.0%)	3 (7.3%)	–	–
Oral mucositis	–	17 (41.5%)	19 (46.3%)	5 (12.2%)	–
Diarrhea	38 (92.7%)	3 (7.3%)	–	–	–
SGOT/SGPT	26 (63.4%)	10 (24.4%)	5 (12.2%)	–	–
Renal					
BUN	34 (82.9%)	7 (17.1%)	–	–	–
Creatinine	36 (87.8%)	5 (12.2%)	–	–	–
Pulmonary	39 (95.1%)	2 (4.9%)	–	–	–
Hair	33 (80.5%)	7 (17.1%)	1 (2.4%)	–	–

8, IV: 19) of 41 (92.7%) primary tumor responded well to this therapy. Only three (7.3%) were histologic poor (Grade I, IIa) responders.

All patients with clinical CRs had good histologic responses. Grade IV histologic regression (no tumor cells remaining in any of the sections) was seen in 17 of 23 (73.9%) patients with CRs. Although good histologic responders among the non-CRs (PRs + NCs) were seen in 15 of 18 (83.3%) patients, there were only two patients (11.1%) who achieved Grade VI histologic regression. There was also no significant difference in histologic response and histologic regression grades on the chemotherapy regimens.

Toxicity

All patients developed mucositis in the external beam radiation therapy field. Grade 2 and 3 mucositis occurred in 46.3% and 12.2% of patients, respectively. Supportive care included enteral nutrition administered through a nasogastric feeding tube in 15 patients. The major hematologic toxicity was leukopenia (48.8%), but it was mild to moderate and reversible. Nausea and vomiting, which was well controlled by antiemetics, occurred in 29.3% of patients. Most of these side effects were expected and were transient (Table VII). Besides, there was no significant difference in the incidence and the grades of toxicities on chemotherapy regimens, but leukopenia occurred slightly more frequently in carboplatin-based chemotherapy. All 41 patients underwent curative surgery after chemoradiotherapy. Surgery was well tolerated and there were no major postoperative complications.

Survival

The Kaplan-Meier estimated 1- and 3-year survival rates for all patients to be 92.7% and 86.8%, respectively. The 5-year cumulative survival rates were 86.8% for all patients, 100% for Stage II patients, 88.6% for Stage III, and 76.4% for Stage IV patients. It should be noted that even in Stage IV patients, a survival rate $> 70\%$ was obtained with this therapy (Fig. 2). When the patient who achieved a CR were compared to those who did not, there was a significant difference in survival (Fig. 3). The 25 complete responders had an estimated 5-year survival of 91.4% vs. 73.9% for non-CRs ($P < .05$).

The relationship between the histologic regression grade and survival was also examined (Fig. 4). Patients who achieved a complete response histologically (Grade IV) had superior survival in comparison to patients with residual tumor in the surgically resected specimen. A better histologic regression grade was associated with a higher survival rate ($P < .05$).

Relapse

Six patients (14.6%) developed recurrent tumors following the surgery. Three patients had locoregional relapse, including one isolated lymph node recurrence. Three patients developed pulmonary metastases without any evidence of local recurrence. All patients with recurrence died after a period ranging from 8 to 22 months.

DISCUSSION

In the last decade, chemotherapy has been introduced in the management of advanced head and neck cancer as part of a multidisciplinary treatment program. Chemotherapy for previously untreated patients with squamous cell head and neck cancer has proven highly effective in inducing significant tumor shrinkage, but, the responses are often incomplete and usually temporary. Some clinical trials have demonstrated that neoadjuvant chemotherapy has failed to produce any survival advantage [10,11] compared to standard treatment without initial chemotherapy. More recent studies have explored the possibility that simultaneous chemotherapy and radiotherapy might be synergistic or at least additive in their effects against head

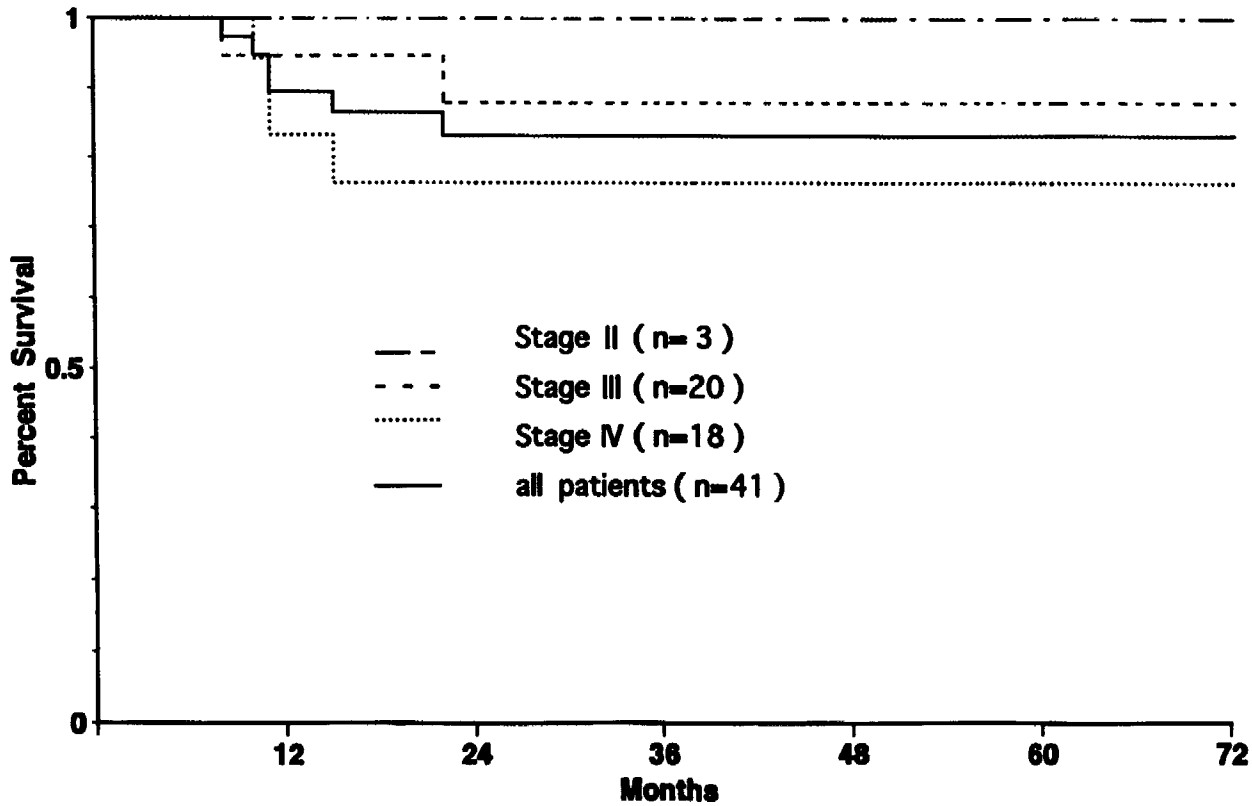

Fig. 2. Overall survival and survival by stage after preoperative chemoradiotherapy and curative surgery. The 5-year cumulative survival rates were 81.5% for all patients, 100% for Stage II, 88.6% for Stage III, and 76.4% for Stage IV patients.

and neck cancer [3]. Tumor-cell kill by each modality separately might be increased from sublethal to lethal events with the combination, thereby preventing the development of resistant tumor-cell subpopulations. Concomitant chemotherapy may prevent the emergence of a highly proliferative cell fraction during radiation.

There are many antineoplastic agents that, when added to radiation, have caused improved disease control over that achieved with radiation alone. These include 5-FU, methotrexate, cisplatin, carboplatin, mitomycin C, bleomycin, and peplomycin (a bleomycin derivative). Cisplatin and carboplatin combined with irradiation have been studied most extensively and have achieved significantly greater response rates in many patients with nonresectable squamous cell carcinomas of the head and neck [5,12]. Moreover, induction chemotherapy using cisplatin-based regimens has produced impressive response rates [13,14]. Slotman et al. [15] have reported overall response rates of 94% for primary tumors using cisplatin-containing chemoradiotherapy. These are among the highest response rates reported for preoperative regimens in advanced head and neck cancer. Their findings of clinical CR in 75% of evaluable primary tumors was superior to the results of preoperative induction chemotherapy regimens and also preoperative sequential chemotherapy and radiotherapy in which clinical CR rates of 6–60% have been reported [16–18]. Our study of chemoradiotherapy achieved a 97.6% response rate (CR 61.0%, PR 36.6%). These excellent clinical overall response and CR rates show that this is a very effective regimen for advanced oral squamous cell carcinoma that compares favorably with previous reports. Moreover, it is unlikely that a CR rate of higher than 60% in advanced oral carcinoma could be produced by chemotherapy or radiotherapy alone. These high response rates for combination therapy suggest a synergistic effect.

However, the overall response rate for patients with clinically positive lymphatic metastases was 50.0% (CR: 13.9%, PR: 36.1%), and the response was generally poorer than that of the primary tumor. If only one metastatic node is noted, some authorities feel that radiation therapy should be used to treat the neck without a neck dissection, but we think our results suggest that cervical metastases are best treated by a radical neck dissection.

Patients receiving intra-arterial infusion and two cycles of chemotherapy tended to have higher clinical CR rates.

Intra-arterial infusion has been used frequently for the treatment of head and neck cancer. This technique tries to achieve maximum drug concentration and selectivity at the tumor site while increasing response and decreasing pharmacologic local and systemic side effects as much as possible. The theoretical basis for the possible advantages of intra-arterial infusion have been reported by Eckman et al. [19]. Recent experiences with the use of intra-

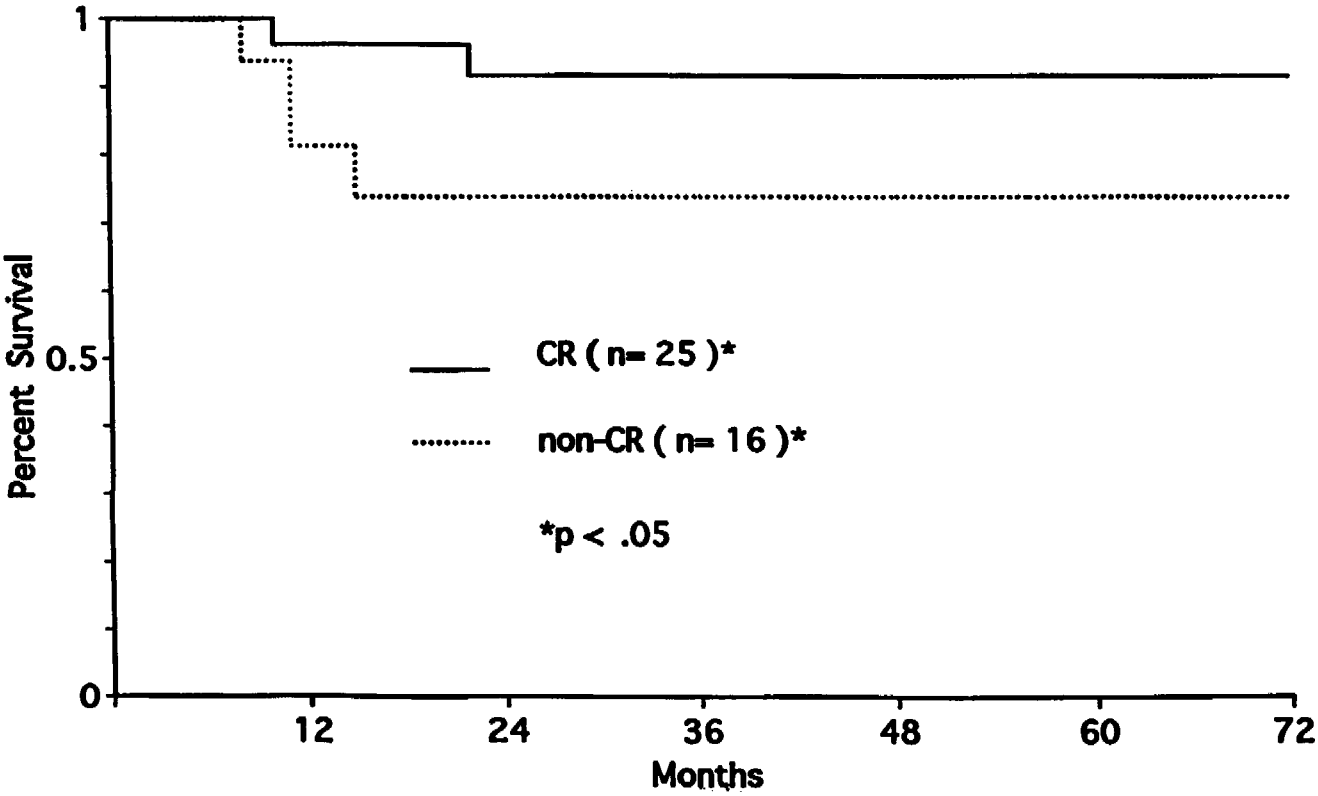

Fig. 3. Overall survival according to the clinical response of the primary tumor, CR or non-CR, to the preoperative chemoradiotherapy. The 5-year cumulative survival rates were 91.4% for CR, 73.9% for non-CR patients. The survival difference is statistically significant ($P < .05$).

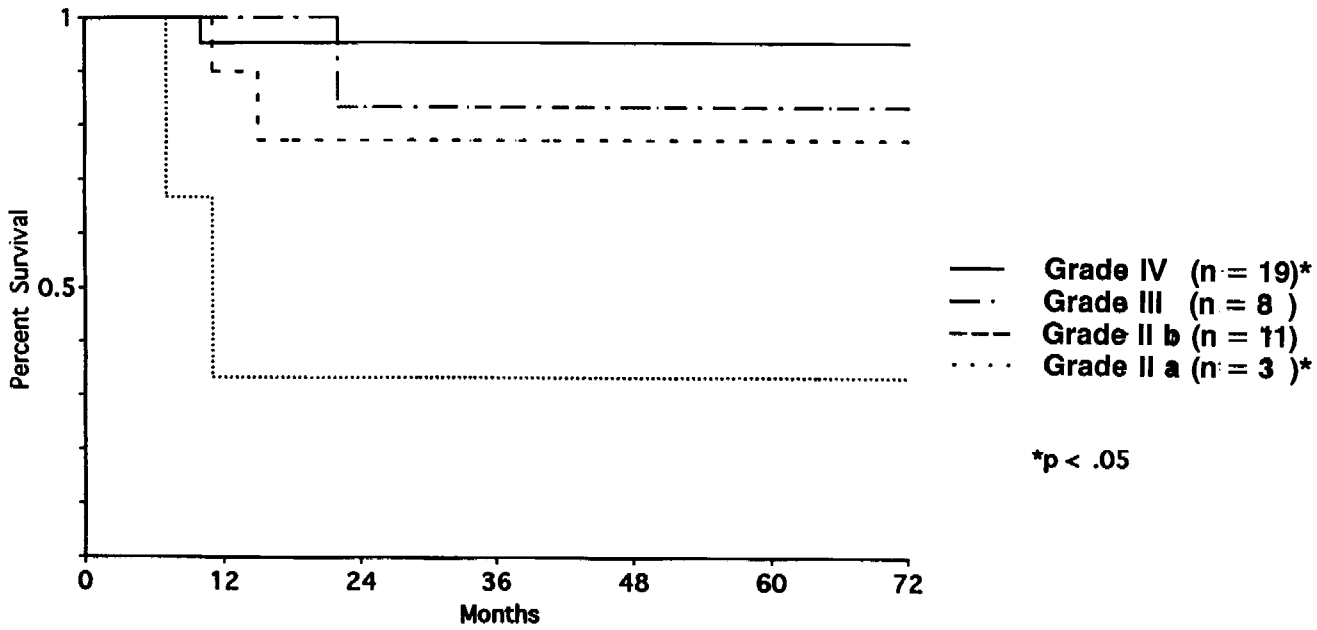

Fig. 4. Overall survival according to the histopathologic regression grade of the primary tumor to the preoperative chemoradiotherapy. Statistical significance: Grade IIa vs. Grade VI, $P < .05$.

arterial cisplatin for advanced head and neck cancers have demonstrated response rates of 47–94% [20–22], and no negative studies have been reported that employ intra-arterial cisplatin. In our experience, 96.5% of patients with oral squamous cell carcinomas responded to intra-arterial infusion of cisplatin-based chemotherapy and radiotherapy. Although the overall response rate to intra-arterial or intravenous infusion was not significantly different in our series, there was a tendency to higher CR rates in patients that received intra-arterial chemotherapy.

Some reports [2,23] have demonstrated that a single cycle of cisplatin-based chemotherapy is not associated with improved survival, disease-free interval, or alterations in the pattern of tumor relapse in patients with potentially curable advanced head and neck cancer. The results in our study suggest that the most effective preoperative cisplatin- or carboplatin-based chemotherapy consists of at least two cycles of chemotherapy given by intra-arterial infusion.

Histopathologic analysis for tumor regression based on the examination of large semiserial sections of the whole surgical specimen according to the grading system of Shimosato and coworkers [8] showed histopathologic CR (Grade IV) in 46.4% of patients after preoperative chemoradiotherapy. This compares favorably with the results of other preoperative cisplatin-based induction chemotherapy regimens in which 5–41% [24,25] histopathologic CRs were achieved. Also, surgical specimens from 73.9% (17/23) of the primary tumors resected after a preoperative clinical CR to chemoradiotherapy were microscopically free of residual tumor (Grade IV). It has been reported that histologic CR were related to the clinical CR and an increase in clinical CR was paralleled by an increase in the number of histological confirmed CRs [25]. Our data lend support to these observations and suggest an improvement over regimens of simultaneous or sequential preoperative multimodality therapy in which few clinical and histologic CRs have been reported [16,26].

The most frequent toxicities in this study were mucositis and leukopenia. Mucositis occurred in all patients, but was considered to be severe (≧ Grade 3) in only 12.2% of the patients treated. Severe leukopenia also was seen in only 4.9%. These toxicities were tolerable and reversible. Minor nausea in several patients was easily controlled. Renal toxicity was not observed in this study. Although mucositis occurred frequently, these results compared favorably with previous reports [3,5,27].

In our series, only 6 of 41 (14.6%) patients were treatment failures and died. Three (7.3%) were due to recurrence of local disease, one (2.4%) was due to the recurrence of regional disease, and the other two patients (4.9%) developed metastatic disease but maintained local disease control until their death. Overall locoregional recurrence was seen in 9.7% of patients. Locoregional recurrence rates after treatment of head and neck cancer with concurrent cisplatin- or carboplatin-based chemotherapy and radiation therapy have been reported to be ~ 36% (range 11–57%) [5,15,28,29] at 2–5 years. This demonstrates the high rate of locoregional tumor control with this approach.

The data presented here suggest the high curability of even advanced oral carcinoma patients using this therapy. The overall survival rate of 86.8% is durable, and higher than 70% survival rates were obtained even in patients with Stage IV disease. These results appear superior to that of past reports in head and neck cancer treatment protocols involving either combined sequential chemotherapy and radiotherapy or adjuvant radiation therapy in which 4- to 5-year survival rates of 23–55% were achieved [15,28,29,30]. Our 5-year surival rates of 88.6% and 76.4% for Stage III and Stage IV patients, respectively, are among the highest rates of cure reported in the treatment of advanced head and neck cancer.

The prognostic value of achieving a clinical CR was clearly demonstrated in this study (Fig. 3). Several studies [3,14,25] have also reported improved survival in patients who achieved clinical CR in comparison to partial or nonresponders, and the CR to induction therapy has now been clearly demonstrated as one of the most important prognostic factors in predicting ultimate disease-free survival. Moreover, it has been reported that clinical CR patients found to have histologic CR at the time of surgery had superior survival compared to those who still had residual disease [28,31].

In this study the correlation between histologic tumor regression grade and the probability of survival was demonstrated. Therefore, we propose the prognosis of patients with pretreated oral carcinomas is dependent upon the histologic grade of tumor regression and that patients with a poor histologic response to preoperative chemoradiotherapy should receive more intensive treatment to the site of the residual tumor. For these patients, additional postoperative irradiation and/or chemotherapy may be appropriate to attempt to reduce locoregional recurrence and distant metastasis.

In summary, our study showed that preoperative simultaneous cisplatin- or carboplatin-based chemotherapy and radiotherapy provided low toxicity, high clinical and histologic response rates, and improved survival compared to historic controls. Therefore, we feel that this regimen may ultimately replace radical surgery in the treatment of advanced oral squamous cell carcinoma.

REFERENCES

1. Suen JY, Newman RK, Hannahs K, et al.: Evaluation of the effectiveness of postoperative radiation therapy for the control of local disease. Am J Surg 140:577–580, 1980.
2. Endicott JN, Jensen R, Lyman G, et al.: Adjuvant chemotherapy for advanced head and neck squamous carcinoma: Final report of the head and neck contracts program. Cancer 60:301–311, 1987.
3. Al-Sarraf M, Pajak TF, Marcial VA, et al.: Concurrent radiotherapy

and chemotherapy with cisplatin in inoperable squamous cell carcinoma of the head and neck. Cancer 59:259–265, 1987.
4. Adelstein DJ, Sharan VM, Earle AS, et al.: Chemoradiotherapy as initial management in patients with squamous cell carcinoma of the head and neck. Cancer Treat Rep 70:761–767, 1986.
5. Zamboglou N, Achterrath W, Schnabel T, et al.: Simultaneous radiation and chemotherapy with carboplatin in inoperable squamous cell carcinoma of the head and neck: A Phase II study. Cancer Invest 10:349–355, 1992.
6. Taylor S, Murthy A, Showel J, et al.: Improved control in advanced head and neck cancer with simultaneous radiation and cisplatin-5-Fu chemotherapy. Cancer Treat Rep 69:933–939, 1985.
7. Crissman JD, Pajak TF, Zarbo RJ, et al.: Improved response and survival to combined cisplatin and radiation in keratinizing squamous cell carcinomas of the head and neck. Cancer 59:1391–1397, 1987.
8. Shimosato Y, Oboshi S, Baba K: Histological evaluation of effects of radiotherapy and chemotherapy for carcinomas. Jpn J Clin Oncol 1:19–35, 1971.
9. Miller AB, Hoogstraten B, Staquet M, et al.: Reporting results of cancer treatment. Cancer 47:207–210, 1981.
10. Foutzilas G, Daniilidis J, Sridhar K, et al.: Induction chemotherapy with a new regimen alternating cisplatin, fluorouracil with mitomycin, hydroxyurea and bleomycin in carcinomas of nasopharynx or other sites of the head and neck. Cancer 66:1453–1460, 1990.
11. Tannock IF, Brouman G: Lack of evidence for a role of chemotherapy in the routine management of locally advanced head and neck cancer. J Clin Oncol 4:1121–1126, 1986.
12. Leipzig B, Wetmore SJ, Putzeys R, et al.: Cisplatin potentiation of radiotherapy. Long-term follow-up. Arch Otolaryngol 111:114–118, 1985.
13. Decker DA, Drelichman A, Jacobs J, et al.: Adjuvant chemotherapy with cis-diaminodichloroplatinum II and 120-hour infusion 5-fluorouracil in stage III and IV squamous cell carcinomas of the head and neck. Cancer 51:1353–1355, 1983.
14. Rooney M, Kish J, Jacobs J, et al.: Improved complete response rate and survival in advanced head and neck cancer after three-course induction therapy with 120-hour 5-Fu infusion and cisplatin. Cancer 55:1123–1128, 1985.
15. Slotman G, Doolittle CH, Glickman AS: Preoperative combined chemotherapy plus radical surgery in advanced head and neck cancer: Five-year results with impressive complete response rates and high survival. Cancer 69:2736–2743, 1992.
16. Mohit-Tabatabai MA, Rush BF, Hill GJ, et al.: Multimodality preoperative treatment for advanced cancer of the head and neck. Am J Surg 148:521–524.
17. Adelstein DJ, Sharan VM, Earle AS, et al.: Simultaneous versus sequential combined technique therapy for squamous cell head and neck cancer. Cancer 65:1685–1691, 1990.
18. Jacobs C, Goffinet DR, Goffinet L, et al.: Chemotherapy as a substitute for surgery in the treatment of advanced resectable head and neck cancer. Cancer 60:1178–1183, 1987.
19. Eckman WW, Patlak CS, Fenstermacher JD: A critical evaluation of the principles governing the advantages of intra-arterial infusions. J Pharmacokinet Biopharm 2:257–285, 1974.
20. Forestiere AA, Baker SR, Wheeler R, et al.: Intra-arterial cisplatin and FUDR in advanced malignancies confined to the head and neck. J Clin Oncol 5:1601–1606, 1987.
21. Milazzo J, Mohit-Tabatabai MA, Hill GJ, et al.: Preoperative intra-arterial infusion chemotherapy for advanced squamous cell carcinoma of the mouth and oropharynx. Cancer 56:1014–1017, 1985.
22. Cheung DK, Regan J, Savin M, et al.: A pilot study of intra-arterial chemotherapy with cisplatin in locally advanced head and neck cancers. Cancer 61:903–908, 1988.
23. Jacobs C, Wolf GT, Makuch RW: Adjuvant chemotherapy for head and neck squamous carcinomas. (Abstr.) Am Soc Clin Oncol 3:182, 1984.
24. Steven DS, Middleton R, Reisch J, et al.: Cis-platinum induction chemotherapy in the multi-modality initial treatment of advanced stage IV carcinoma of the head and neck. Cancer 51:2168–2174, 1983.
25. Al-Kourainy K, Kish J, Ensley J, et al.: Achievement of superior survival for histologically negative versus histologically positive clinically complete responders to cisplatin combination patients with locally advanced head and neck cancer. Cancer 59:233–238, 1987.
26. Taylor SG, Murthy AK, Caldarelli DD, et al.: Combined simultaneous cisplatin/fluorouracil chemotherapy and split course radiation in head and neck cancer. J Clin Oncol 7:846–856, 1989.
27. Weissler MC, Melin S, Sailer SL, et al.: Simultaneous chemoradiation in the treatment of advanced head and neck cancer. Arch Otolaryngol Head Neck Surg 118:806–810, 1992.
28. Chougule PB, Suk S, Chu QD, et al.: Cisplatin as a radiation sensitizer in the treatment of advanced head and neck cancers: Results of a phase II study. Cancer 74:1927–1932, 1994.
29. Marcial VA, Pajak TF, Mohiuddin M, et al.: Concomitant cisplatin chemotherapy and radiotherapy in advanced mucosal squamous cell carcinoma of the head and neck: Long-term results of the radiation therapy oncology group study 81–17. Cancer 66:1861–1868, 1990.
30. Jacobs JR, Fu KK, Lowry LD, et al.: 5-year results of cisplatin and fluorouracil infusion in head and neck cancer. Arch Otolaryngol Head Neck Surg 117:288–291, 1991.
31. Mohr Ch, Bohndorf W, Carstens J, et al.: Preoperative radiochemotherapy and radical surgery in comparison with radical surgery alone. A prospective, multicentric, randomized DÖSAK study of advanced squamous cell carcinoma of the oral cavity and the oropharyx (a 3-year follow-up). Int J Oral Maxillofac Surg 23:140–148, 1994.